Modeling the Impact of Proliferation and Attrition on the Memory T-Cell Repertoire

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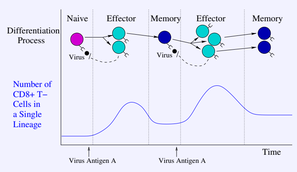
Abstract

New infections change an individual's protective immunity to past diseases by inducing cellular proliferation and attrition events that alter the composition of the memory T-cell compartment. For instance, viral infections both introduce new lineages into the memory repertoire and deplete existing lineages through direct or bystander effects. We quantify how particular proliferation and attrition events impact the memory CD8$^+$ T-cell repertoire using a combination of Markov processes and probability distributions. This provides insight into how the immune memory repertoire as a whole is affected by individual lineage dynamics.

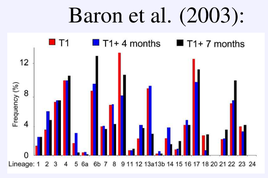
Biological Background

- CD8$^+$ T-cells: immune cells that kill infected host cells
- T-cell lineage: all T-cells with the same T-cell receptor (antigen specificity)
- Memory T-cell repertoire: size and distribution of memory T-cell lineages

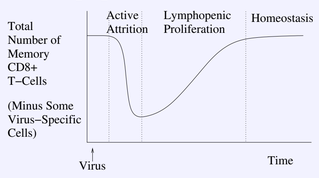


A Subset of the Memory Repertoire

Baron et al. (2003):



Some virus infections cause a drastic decrease in memory CD8$^+$ T-cells early in infection in a process called active attrition [2].



Active attrition is followed by lymphopenic proliferation (also known as homeostatic proliferation), in which surviving memory cells and naive cells that differentiate directly into memory cells refill the memory CD8$^+$ T-cell compartment [3].

Our Question

The make-up of the memory repertoire determines which infections are met with efficient immune responses. Active attrition induces a within-host bottleneck of the memory CD8$^+$ T-cell population that could permanently alter the host's immunity to many infections. Therefore, we ask:

What is the impact of active attrition and subsequent lymphopenic proliferation on the memory CD8$^+$ T-cell repertoire?

Notation & References

Definition	Vector	Entries	Sum	Length
Initial memory repertoire	$\vec{m}$	m_i	m_c	M
Repertoire of newly differentiated naive cells	$\vec{n}$	n_i	n_c	N
Memory repertoire following active attrition	$\vec{a}$	a_i	a_c	M
Repertoire of total cells during lymphopenic proliferation	$\vec{s}$	s_i	s_c	$M+N$
Final memory repertoire ($\vec{z}=\vec{s}$ when $s_c=m_c$)	$\vec{z}$	z_i	m_c	$M+N$
Unit vector with 1 in position i and 0 elsewhere	$\vec{e_i}$		1	$M+N$

[1] Baron et al. (2003) *The Repertoires of Circulating Human CD8$^+$ Central and Effector Memory T-Cell Subsets Are Largely Distinct*. Immunity 18, 193.

[2] Selin et al. (2006) *Memory of Mice and Men: CD8$^+$ T-Cell Cross-Reactivity and Heterologous Immunity*. Immunol. Rev. 21, 164.

[3] Almeida et al. (2005) *Homeostasis of T-Cell Numbers: From Thymus Production to Peripheral Compartmentalization and the Indexation of Regulatory T-Cells*. Sem. Immunol. 17, 239.

Active Attrition (AA) Model

We use a multivariate hypergeometric distribution to find the probability that active attrition results in a particular repertoire. We assume:

- Active attrition causes an 80% reduction in memory cells. ($a_c = 0.2m_c$)
- Naive cells contributing to lymphopenic proliferation do not undergo AA.

$$Pr(\vec{a}|\vec{m},a_c)=\begin{cases}\dfrac{\prod_{i=1}^{M}\binom{m_i}{a_i}}{\binom{m_c}{a_c}} & \text{if } \sum_{i=1}^{M}a_i=a_c\\ 0 & \text{if } \sum_{i=1}^{M}a_i\neq a_c\end{cases}$$

Lineage extinctions only occur during active attrition, so the probability that lineage i goes extinct can be calculated from $Pr(\vec{a}|\vec{m},a_c)$ with $a_i=0$.

Unweighted Lymphopenic Proliferation (LP) Model

We model lymphopenic proliferation with an event-based Markov birth process that tracks cell divisions as the memory compartment refills. We assume:

- All cells are equally likely to proliferate.
- Both memory cells and newly differentiated naive cells can contribute.
- LP stops when the memory compartment refills to m_c cells.

Event-based Markov birth process:

$$Pr(\vec{s}|\vec{a},\vec{n},m_c)=\begin{cases}1 & \text{if } s_c=a_c\\ \sum_{i=1,\ s_i-a_i\neq 0}^{M+N}Pr(\vec{s}-\vec{e_i}|\vec{a},\vec{n},m_c)\left(\dfrac{s_i-1}{s_c-1}\right) & \text{if } s_c\leq m_c\\ 0 & \text{if } s_c>m_c\end{cases}$$

We analytically show that this multivariate negative hypergeometric distribution solves the birth process:

$$Pr(\vec{s}|\vec{a},\vec{n},m_c)=\frac{\prod_{i=1}^{M}\binom{s_i-1}{s_i-a_i}\prod_{i=1}^{N}\binom{s_i-1}{s_i-n_i}}{\binom{s_c-1}{s_c-a_c-n_c}} \text{ if } a_c+n_c\leq s_c\leq m_c$$

For example, with one memory lineage and one naive lineage:

$$\begin{aligned}Pr(s_1,s_2|a_1,n_1,m_c) &= Pr(s_1-1,s_2|a_1,n_1,m_c)\left(\tfrac{s_1-1}{s_1+s_2-1}\right)\\ &\quad +Pr(s_1,s_2-1|a_1,n_1,m_c)\left(\tfrac{s_2-1}{s_1+s_2-1}\right)\\ &= \frac{\binom{s_1-1}{s_1-a_1}\binom{s_2-1}{s_2-n_1}}{\binom{s_1+s_2-1}{s_1+s_2-a_1-n_1}}\end{aligned}$$

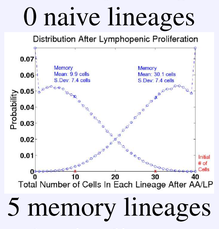
Unweighted AA/LP Results

The memory CD8$^+$ T-cell repertoire resulting from active attrition and lymphopenic proliferation is governed by the probability distribution:

$$Pr(\vec{z}|\vec{m})=\sum_{\{\vec{s}=\vec{z}\}}Pr(\vec{s}|\vec{a},\vec{n},m_c)Pr(\vec{a}|\vec{m})$$

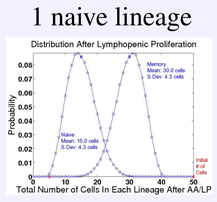
Sampling from this distribution gives the following results:

2 memory lineages
0 naive lineages



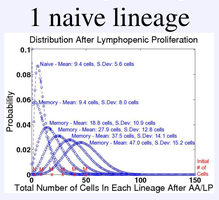
SI: 0.62
→ 0.69

1 memory lineage
1 naive lineage



SI: 1
→ 0.46

5 memory lineages
1 naive lineage



SI: 0.239
→ 0.235

Simpson's Index (SI) is the probability that two randomly chosen cells are identical.

Weighted LP Model

To model lymphopenic proliferation in the case that some cells are more likely to proliferate than others, we assume each lineage proliferates independently except at the last cell division.

- By solving a Yule process, we find:

$$Pr(s_i,t|a_i,t_0,w_i)=\binom{s_i-1}{s_i-a_i}e^{-\beta w_i a_i t}\left(1-e^{-\beta w_i t}\right)^{s_i-a_i}$$

when $s_c < m_c$, where $t_0=0$, β is the number of divisions per dividing cell per time, and lineage i has proliferation weight w_i.

- We then solve a weighted Markov birth process to find the joint probability distribution for the final cell division. For instance, with two memory lineages:

$$Pr(s_1,s_2,t|\vec{a},0,\vec{w})=\beta\tbinom{s_1-1}{s_1-a_1}\tbinom{s_2-1}{s_2-a_2}\cdot \sum_{i=1}^{2}\left[w_i(s_i-a_i)\int_0^t e^{-\beta(w_1a_1+w_2a_2)x}\left(1-e^{-\beta w_i x}\right)^{s_i-a_i-1}\left(1-e^{-\beta w_j x}\right)^{s_j-a_j}dx\right]$$

where if $i=1$, $j=2$ and vice versa.

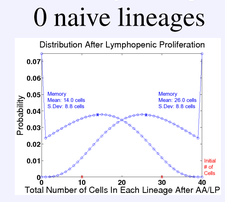
- Finally, we show that the overall joint probability distribution is an exact solution to weighted LP case.

Weighted AA/LP Results

We combine the active attrition and weighted LP models to find the final memory CD8$^+$ T-cell repertoire.

- The weighted AA/LP results with $\vec{w}=\vec{1}$ match the unweighted AA/LP results.
- Qualitatively, weighting cell proliferation affects the final repertoire as expected. (Lower-weighted lineages are smaller and higher-weighted lineages are larger than if the weights were equal.)
- Quantitatively, we can exactly find the probability distribution for the final size of each lineage.

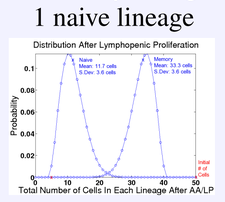
2 memory lineages
0 naive lineages



$w_1 : 1$
$w_2 : 0.7$

SI: 0.62
→ 0.63

1 memory lineage
1 naive lineage



$w_1 : 1$
$w_2 : 0.7$

SI: 1
→ 0.51

Conclusions

We can exactly predict the probability distributions for the memory CD8$^+$ T-cell repertore that results from active attrition and lymphopenic proliferation.
Also, if only memory cells contribute to proliferation:

- After active attrition and unweighted lymphopenic proliferation, the memory repertoire on average matches the initial repertoire, although the distributions are skewed such that large lineages become larger and small lineages become smaller.
- When proliferation is weighted, the means and skews change based on the weights.
- Diversity of the memory repertoire decreases if the weights are sufficiently close.

If newly differentiated naive cells contribute to lymphopenic proliferation:

- Memory lineages decrease in size on average as newly differentiated naive cells are introduced.
- Diversity of the memory repertoire increases due to migration of new lineages from the naive repertoire.

Future Directions

- If possible, verify the results against biological repertoire data.
- Apply the models to see how a "normal" acute viral infection impacts the memory CD8$^+$ T-cell repertoire.